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# CLINICAL PROCEEDINGS

OF THE

AMERICAN MEDICAL ASSOCIATION

CHICAGO, ILL., MAY 1915

REPORT OF THE

COMMISSIONERS OF THE

AMERICAN MEDICAL ASSOCIATION

ON THE

PROCEEDINGS OF THE

AMERICAN MEDICAL ASSOCIATION

AT CHICAGO, ILL., MAY 1915

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## THE PSYCHOGENIC ASPECTS OF BRONCHIAL ASTHMA

Robert Scanlon, M.D.\*

It is not the purpose of this paper to attempt to prove or to disprove the importance of the psychogenic factors in bronchial asthma. Rather, its intention is to present the observations of many writers who are interested both in the fields of allergy and psychiatry, or more accurately, in the field of psychosomatic medicine. The ultimate intention, therefore, is to familiarize readers interested in the problem of bronchial asthma with the aforementioned observations so that they may apply them and possibly attain alleviation or elimination of asthmatic episodes in their patients.

In the past, one of the main obstacles to psychosomatic medicine was the refusal by many workers to acknowledge the fact that the mind and the body were very much integrated. However, this barrier now seems to be almost eliminated so that, as Glaser<sup>1</sup> writes, "no one now seriously questions the important role of the psyche in human disease of any kind."

This new awareness is further illustrated by a questionnaire sent to various physicians interested in the problem of bronchial asthma in an effort to obtain their feelings as to the importance of the psyche in this condition. It was reported as follows:<sup>2</sup>

1) Do you find psychological techniques helpful in the treatment and diagnosis of bronchial asthma?

Yes—300

No—93

No answer—31

2) Would you care to see how others apply psychologic techniques?

Yes—433

No—17

No answer—4

This new interest is reflected in the fact that more studies concerning bronchial asthma are being reported and that included in these studies is the possible role of the psychogenic factor.

Bronchial asthma carries more than slight social import. Williams<sup>3</sup> states that asthma is as common a cause of disability as gastric and duodenal ulcers combined; he continues by stating that it is commoner than all fractures and commoner than hypertension, angina pectoris and vascular heart disease combined, and that it induces nearly twice the incapacity of all forms of tuberculosis. His survey of 1,000 college students revealed 53 asthmatics, 17 of whom had active asthma. The over-all

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mortality rate of bronchial asthma is approximately 0.6 per cent of all deaths<sup>3</sup> with the vast majority of deaths occurring predominantly in the middle age and elderly age groups (usually in those with chronic asthma or in those prone to status asthmaticus).<sup>4</sup> However, this mortality rate varies, as exemplified by the rate of 12 per cent in a small midwestern city of 50,000 population where morphine or morphine derivatives were frequently used.<sup>5</sup>

Who gets asthma? Is asthma hereditary? Is asthma a conditioned response? Does asthma have one etiologic factor? It is felt by some<sup>6</sup> that bronchial asthma is basically allergic in origin but, once the pattern is set up, emotional tensions may precipitate an attack. Others<sup>7</sup> feel that allergens are only one of the many precipitating factors and that in order to become effective they require a special constitution and a special conditioning. This thought of acquired conditioning is put forward by Dekker and Groen<sup>8</sup> who note that even though the patient was aware of a particular stimulus (in this instance, psychogenic) he could not prevent an attack when the stimulus was presented to him. Gillespie<sup>9</sup> becomes specific when he states that asthma is a conditioned response to a stimulus with psychologic association.

It has been reported that asthmatics present a positive family history in 50 per cent of cases.<sup>10</sup> Rees<sup>11</sup> found in his series that all asthmatic groups excepting male patients under 16 years of age have a significantly higher incidence of asthma, hay fever, vasomotor rhinitis and flexural eczema in parents and siblings. However, age seems to be important in respect to heredity since there appears to be a higher incidence of asthma in the family when the initial attack occurs in childhood: the older the patient at the onset of asthma, the less the likelihood of a positive family history.<sup>12</sup>

In a study of monozygotic twins reported by Bowen<sup>13</sup> a few years ago, among 59 pairs of identical twins there were only seven pairs with *bilateral* allergy, leaving 52 pairs in which only one twin had an allergy.

Is there one main etiologic factor? In most cases, probably not. A particular case of bronchial asthma will probably have a combination of etiologic factors. It is generally considered that the three main categories of etiologic factors are allergic, infectious, and psychogenic. Rees<sup>11</sup> in his study of 441 patients found that a multiple etiology was present in many cases and noted that in these patients psychologic factors were present in 70 per cent, infection in 68 per cent and an allergic phenomenon in 36 per cent. Maxwell<sup>14</sup> in a study of 150 cases reported that only 28 cases showed one factor, whereas 122 cases had two or more factors present. These reports only intensify the necessity of broadening one's view of bronchial asthma. There have been numerous articles which substantiate the fact that if one is sensitive to a certain substance, for example, pollen or dust,

and one is exposed to this substance, he is very likely to have a reaction, such as an asthmatic attack. There are also many reports of asthmatic attacks caused by severe emotional stress in apparently nonallergic individuals. Certainly infection preceding asthmatic attacks is a frequent occurrence. Therefore, these reports and those demonstrating multiple factors seem to imply a synergism among these three main factors.<sup>2, 11, 15</sup>

The importance of each factor varies with each series. Advocates of infectious etiology stress the importance of multiple chest infections, 60 per cent in some series;<sup>10</sup> Gottlieb<sup>4</sup> quotes Flensburg who found that of 450 cases, 55 per cent had frequent colds, 33 per cent had laryngitis, 16 per cent had a history of measles or pertussis, and 9 per cent had had pneumonia. The history of infection previous to asthmatic episodes and the cessation of attacks following desensitization with stock vaccine is well known. Possible foci of infection may be in the tonsils and adenoids.<sup>16</sup>

The great importance of allergens is generally recognized and need not be discussed.

The role of psychiatry is being accepted more and more. Schwoebel<sup>7</sup> reported in his study of 142 cases that some psychogenic factor was present in all cases: he stated that 36 patients told of a precipitating emotional factor in the first attack; 28 cases later in treatment remembered an emotional factor precipitating the first attack; and 78 patients could not remember a precipitating emotional cause in the first attack but could recall a psychogenic factor in later attacks.

Treuting and Ripley<sup>17</sup> also stressed the importance of the psychogenic factor in five case studies. Their patients all had seasonal asthma with positive skin tests to pollen and ragweed. The authors could precipitate attacks of asthma during the psychologic interview. Such precipitation of asthmatic attacks during interviews or playroom sessions has been noted by others.<sup>18</sup> Further, it has been noted that when attacks are eliminated by psychotherapy the positive skin reactions remain.<sup>19</sup>

Wittkower<sup>20</sup> cites instances where allergies were suggested while individuals were under hypnosis and these allergies were found to occur in the waking state. The skin tests were negative in these cases and there was no previous history of asthma. He also relates a case of tobacco allergy (causing asthma) which was inhibited by hypnotic suggestion. Wittkower also quotes a case of Diehl and Heinicher who succeeded in changing the size of an allergic skin test by 40 per cent via hypnosis and suggestion. Gillespie<sup>9</sup> relates cases of asthma that were stopped by placebos only.

Treuting and Ripley<sup>17</sup> also tried suggestion and noted its effect on acute asthmatic episodes. They gave sodium amytal intravenously and by interview established feelings of security in the patient. It was noticed shortly thereafter that the attacks were ameliorated or dispelled. When

they gave the sodium amytal intravenously to asymptomatic patients and recalled sources of emotional tension obtained by history, they precipitated attacks of asthma.

Thus it is suggested that not only can attacks be initiated by emotional stress and at times by suggestion (as during interviews and hypnosis) but that some asthmatic attacks with a dual component of allergic and psychogenic factors can be decreased or eliminated by recognition of the psychic problems.

Is there any relationship between age and sex and the apparent main etiological factor? Maxwell<sup>14</sup> claims that allergy is the principal etiologic factor in childhood but that the psychogenic factor is the most important in all age groups. Others<sup>1,6</sup> believe that infection is the most important factor in childhood. Rees<sup>11</sup> in his work tabulated the following initial precipitating causes:

	Infection	Allergy	Psychologic
Children	55%	20%	25%
Adults	45%	20%	35%

Rees found that in female patients the psychologic factors increase with age; in male patients aged between 16 and 35 years the psychologic factors decrease in importance but after the latter age their importance increases. In regard to elderly and middle aged asthmatics, Rackemann<sup>21</sup> feels that that psychosomatic factors and infection are the most important. Rees<sup>22</sup> concludes that in this age group psychogenic factors are the most important and allergenic factors the least important. In short, the general feeling has been that allergy and/or infection are most important in childhood, and that infection and the psyche are most important in middle aged and elderly individuals. But now, as noted, the importance of the psychogenic factor in childhood is being recognized more and more.

Is there any relationship between age at onset and the sex of the patient? It has been reported that 63 per cent of male patients start having their asthmatic attacks below 16 years of age, as compared with 50 per cent of female patients. Between the ages of 16 and 45 years, a higher percentage of female than male patients have their first attack of asthma.<sup>3, 11</sup> Over-all, there are approximately twice as many male as female patients below 16 years of age suffering from asthma, while over 16 years of age there is a preponderance of women.<sup>3, 11</sup>

Bronchial asthma is often considered to be closely related to the hypothalamic-pituitary-adrenal axis, this axis often being mentioned as the neural pathway for psychic influence.<sup>1, 11</sup> Furthermore, autonomic imbalance of the vagal type also has often been mentioned as a major factor in many cases of asthma; its importance is exemplified by the fact that in

some cases resection of the vagus nerve through the posterior pulmonary plexus afforded relief from asthma.<sup>12</sup> As Wolf<sup>23</sup> states: "Asthma is an antigen-antibody response occurring in the respiratory tree but the reaction may result just as readily from cholinergic neural impulses still essentially reversible but capable of producing symptoms, complications and even death." He feels, however, that allergy is not a neural response since tissue sensitivity may be demonstrated in denervated areas and even in excised tissue. But he further states that the response of the tissue to the antigen-antibody reaction may be markedly influenced by neural and other forces acting at the same time. This, then, could be an explanation for the possible synergism. Also in this regard, some feel that emotional tension can produce changes which are conducive to infection in the bronchial mucosa (possibly via neural pathways).<sup>11</sup> This, too, could theoretically explain synergism.

Steele<sup>12</sup> proposes another theoretical consideration: he feels that there exists in asthmatics a functional suppression of the adrenal cortex (glucocorticoid hormones) which is a result of heredity. The adrenal cortex is one of the main adaptive forces of the body and this suppression results in deviation from the homeostatic state. He defines the homeostatic state as a perfect equilibrium between bodily stresses (somatic and psychic, internal and external) and the adaptive forces of the body. Steele does not feel that there is an inherent bronchial weakness.

If this theory be true, perhaps bronchial asthma could be explained as follows: an antigen-antibody response and/or infection results in a temporary defect in the respiratory tree. If the reaction is severe enough and the body is thus in a stress state, then, due to functional adrenal cortical suppression, a relative adrenal insufficiency would result and an asthmatic episode be precipitated. Or again, if the antigen-antibody reaction or the infection were not so severe as to cause a reaction, then, perhaps, a superimposed psychogenic factor and resultant emotional stress could also cause increased body stress and relative adrenal cortical insufficiency (i.e., an insufficiency of the glucocorticoid hormone), and thus produce an asthmatic attack. If the reaction were severe enough, the primary effect of epinephrine on the respiratory tree would be insufficient and therefore, epinephrine fastness would occur. Steele<sup>12</sup> postulates further that the glucocorticoid hormone is related to the blood sugar, as the mineralocorticoid hormone is related to the body sodium. There might be a glycogen depletion in the acute asthmatic because of a decrease in the glucocorticoid hormone. This would explain (a) epinephrine fastness, and (b) the improvement of some individuals on dextrose water (in addition to the hydrating effect).

Are there any physiologic changes in the asthmatic patient? Certain

physiologic studies were performed on the respiratory function of asthmatic patients. Doust and Leigh<sup>10</sup> demonstrated that oxygen saturation levels and respiratory efficiency scores are in the low normal range, almost pathologically low. Therefore, minimal stress can lead to anoxemia as can emotional tension. (Paradoxically, simulated asthmatic breathing by a normal person actually increases oxygen saturation.) In additional studies the vital capacity was normal to moderately reduced<sup>24</sup> and the maximum breathing capacity was also reduced.<sup>25</sup>

Other experimental work was done using acetylmethylcholine on psychotic patients. It was found that in nonpsychotic asymptomatic asthmatic patients this drug would precipitate a severe asthmatic reaction. It was also noted that psychotics very seldom had an asthmatic episode regardless of whether they had asthma in the prepsychotic period. When acetylmethylcholine was given to these psychotics, no asthmatic attack was precipitated. This was interpreted as meaning (a) that psychotic patients had increased secretion of adrenalin or, (b) that they had completely withdrawn, thus "solving" their conflicts and thus eliminating the psychogenic factor of their asthma; they seemingly had "resolved" the emotional stress that had influenced asthmatic attacks.

But what constitutes emotional stress? A large variety of causes have been shown to precipitate an asthmatic attack, ranging from joy and elation to deep frustration.<sup>11</sup> Doust and Leigh<sup>10</sup> state that *three* main psychogenic factors may induce an attack: maternal rejection, maternal separation, or rage or fear. Dekker and Groen,<sup>8</sup> attempting to determine what constitutes emotional stress, tested the vital capacity of asthmatics when they were exposed to traumatic emotional experiences uncovered in the history. They reported a decrease in the vital capacity associated with typical asthmatic dyspnea and relief with the use of epinephrine. They felt that these emotional stresses were definitely related to previous life trauma and stated that the attacks were indistinguishable from those episodes precipitated by allergen inhalation. This study did not define specifically what constitutes emotional stress, but it did show that emotional trauma occurring earlier in life could precipitate an attack.

Are all emotional stresses capable of precipitating an attack? Ostensibly not; in fact, apparently innocuous stimuli (the picture of a goldfish or a horse) were found to be capable of inducing an attack, while emotional strains that appeared severe to the examiner surprisingly had no effect on the patients.<sup>11</sup> Actually, what appears to be important in precipitating an asthmatic episode is not only emotional tension but the specific importance that this tension has to the patient.<sup>11, 26</sup> To stress this point further, a group of medical students who were known asthmatics were studied under conditions that appeared very stressful: immediately before intern an-

nouncements and before important examinations. At these times there was no wheezing. However, when instances of previous life trauma were introduced, asthmatic episodes developed.

Definite personality types have often been attributed to asthmatic patients. However, much has also been written as to the personality makeup of the mother of an asthmatic child. Naturally the description that follows is not universal since there are many exceptions. Bakwin<sup>6</sup> states: "Many allergic children doubtless have mothers whose personalities are not so rigid and these children can adapt better to their environment. In these instances the psychogenic factors play a less important part or none at all."

In a recent study<sup>11</sup> it was noted that the most common contributory parental trait was overprotection; rejection and perfectionism occurred less frequently. This is in agreement with Bakwin<sup>6</sup> who reported that parental overprotection played a major role in 17 of his 23 cases of asthma. The experience of Gillespie<sup>9</sup> is similar. The overprotection has been described as being hostile and demanding ("I do so much for you, I expect you to do a lot for me in return.")<sup>27</sup>

However, in many other studies the major role was found to be maternal rejection. Glaser<sup>1</sup> writes that maternal rejection is probably the most important psychologic factor. Here, maternal rejection is defined as a feeling of the loss of the mother by the child whether that be by outward rejection or separation of the child from the mother due to business, death, marital difficulties or the birth of another child producing sibling rivalry. Others<sup>27</sup> define maternal rejection as a variety of attitudes which demonstrate the mother's dissatisfaction with the child and with her having him. However, regardless of the many forms of rejection, there is always the underlying fear in the child that the mother may not love him and may leave him. Other reports claim that besides maternal rejection there is another facet in the maternal personality: the mother attempts to force the child into what she thinks is best for the child, this pattern perhaps reflecting the parent as she would like to be. However, when the child fails to meet these demands, he is rejected.<sup>3</sup>

Miller and Baruch<sup>28</sup> performed an interesting study in an attempt to determine if there was a higher incidence of maternal rejection among allergic children than among nonallergic children. They reported that maternal rejection was present in 98 per cent of the allergic children but only in 24 per cent of the nonallergic individuals. Therefore, on the basis of this one study the presence of this factor is apparent.

But some, in questioning rejection, ask why some children appear to occupy a ~~significant place~~ <sup>significant place</sup> in the family; that is, an oldest child or a youngest child. ~~Some investigators~~ <sup>Some investigators</sup> found that in many of these cases the parents

actually did not want the child and thus developed a guilt complex and resultant overcompensation by overprotection.

How, then, can these differences in reports be explained; some maintaining overprotection, others rejection? Mitchell, et al.,<sup>29</sup> made a very interesting observation in this regard. It was noted in their study that very often two workers interviewing a mother at different times would get a different opinion as to the mother's personality, one noting an overprotective attitude, another noting one of rejection. Upon further investigation, they found that this was a true observation and was explained by the fact that the mother's feelings usually oscillated between one of utmost concern for the child to one of rejection. Thus, these two characteristics of overprotection and rejection may readily be found together, but may appear separately at varied times.

Are there any other traits in the mother of asthmatic children that one may recognize as contributing to the child's emotional tension? The mothers are often described as being capable and competent but often carry the feeling of being threatened if they are not masters of a situation; they are usually bossy and dominant in the home;<sup>6, 29</sup> some may give little affection to the husband or child but over-all they are usually conscientious in their duties toward home and family.<sup>30</sup> The mothers usually set high goals for themselves and their children.<sup>31</sup> They are further described as being ambitious for themselves and for their children.<sup>32</sup>

There is not much written about the father of the asthmatic child. Here, too, it must be kept in mind that, as in the case of the mother, many fathers do not fit the following description. Mohr, Gerard and Ross,<sup>32</sup> characterize the father as not being actively interested in the children and playing but a small part in their training and care. Other writers<sup>29</sup> describe the fathers as holding a weak place in the family, either due to sickness, separation or death. These thoughts seem to agree with the above observation of the mother being the dominant parent.

Is there a type specific personality for the asthmatic child? It was previously thought that asthmatics have a cyclothymic personality,<sup>19, 33</sup> but recent reports cannot support this conclusion.<sup>11, 26</sup> Rees<sup>11</sup> states that generally, asthmatics have marked anxiety, marked timidity, marked sensitiveness, marked obsessional traits, and a higher incidence of neurotic conditions than nonallergic individuals. He feels that these traits set up emotional tension states which can precipitate an attack. Others<sup>7</sup> state that individuals who develop asthma are those with a constitution of nervousness and anxiety and a tendency to hypochondriasis and inferiority feelings; these individuals tend to be egocentric, stubborn and to retreat into sickness if things do not turn out as desired. Self-confidence also appears to be less in asthmatic patients.<sup>6, 7, 34</sup>

Schwobel<sup>7</sup> feels that the most prevalent character trait is a fear which is a deep-seated anxiety, and that most of the asthmatic's actions are determined by this fear. The egocentric tendencies which are present in the asthmatic tends to disable him when he attempts to perform a specific task. In short, his anxieties along with his unwillingness to take risks and his lack of steadiness tend to prevent him from fulfilling many of his wishes; all these traits tend, therefore, to cause him to become very dependent upon others.

Dunbar<sup>19</sup> feels that asthmatics are obsessive-compulsives, but there are very few phobias in these patients;<sup>19, 26</sup> she states that, in addition, asthmatics have an intense hostility and aggressiveness, are ambitious, hyperactive, and show much self-concern. The asthmatic sufferer, too, uses this excessive conscientiousness as a means of satisfying the need for praise and prestige. In this way he decreases his anxiety and tension.<sup>17</sup> The striving for recognition and prestige is also reflected by some patients who emphasize intellectual accomplishments.<sup>36</sup> This fairly rigid intellectual control helps the patient to repress his anxiety.<sup>35</sup> It should be mentioned here that contrary to early reports<sup>9, 27</sup> the asthmatic patient does not have superior intelligence but is generally rated in the group of average intelligence.<sup>17, 29, 36, 38</sup>

Others find that asthmatics have a tendency toward depression.<sup>9, 10, 35</sup> Mitchell, et al.,<sup>29</sup> found that younger children tended to show signs of motor inhibition while older children, particularly girls, showed signs of emotional depression as well as hysterical manifestations.

Probably one of the main personality traits of the asthmatic child is his marked dependency upon his mother. There appears to be an intense need for parental love and protection and an almost constant fear of losing the mother's support and love.<sup>39</sup> These feelings of dependency were illustrated by psychologic tests.<sup>36</sup> French and Alexander and others feel that it is in this area that the main conflict arises: the child has ambivalent feelings, characterized by a protest against separation and a protest against the necessity of dependency.<sup>29, 32, 40</sup> Thus it is readily noted that these dependent feelings and needs as well as the other factors already mentioned result in manifest feelings of insecurity in the asthmatic. How does this affect or precipitate an attack? Ordinarily when a child is insecure he becomes resentful and shows it by work or behavior.<sup>41</sup> However, asthmatics cannot show their resentment because of their marked dependency and their fear of losing the regard and recognition of others, particularly the love and support of the mother.<sup>29, 41</sup> Therefore, instead of outwardly showing their resentment and hostility they turn it in on themselves;<sup>29</sup> that is, they "bottle it up."<sup>11</sup> Most children attempt to adjust to the dominating personality of the mother by submission or open rebellion.<sup>6</sup> Asthmatics

tend toward submission with the result as described above. Therefore, any threat of separation from the mother, such as open maternal rejection, punishment, birth of a new baby, sibling rivalry, etc., tends to increase the feelings of insecurity and thus to increase the feelings of resentment.

Further evidence for a possible psychic role is illustrated by the following: If individuals have a marked amount of emotional conflict they will block during psychologic interviews. Since asthmatics are considered to have many emotional conflicts, do they block during interviews? Miller and Baruch<sup>28</sup> in a study of 90 asthmatic children found that 92 per cent of allergic children blocked during the testing but only 17 per cent of a non-allergic group did so. They also found that 92 per cent of children who were rejected had blocked but that none of the 13 nonallergic children who were rejected had blocked.

Besides the reasons listed above, other writers<sup>6</sup> feel that asthmatic attacks are precipitated in two other ways: (a) the child is aware of the agitation produced by his attacks and the worry exhibited by his parents so that he finds his illness a ready means of getting his own way and of evading responsibilities. This choice may be conscious or unconscious. It is as if he were saying "I will have an attack if I can not do so and so." Or, (b) the child may use his attacks of asthma as a release for his guilt feelings; by becoming ill he hurts himself and thus repents for his guilt.

Finally, others have regarded the asthmatic attack as equivalent to anxiety or rage that has been inhibited;<sup>42</sup> that is, anger often precipitated attacks when it could not be expressed and was followed by feelings of inadequacy and frustration.

In conclusion it must again be stated that not all asthmatics and their parents fit the above descriptions. This is exemplified by the fact that a few of these children resent parental coddling and restrictions and become antagonistic, disobedient and resentful; they are fidgety, destructive, and poorly disciplined and often make poor school adjustments. In some instances they do well away from home; here they are free from allergens and a highly charged atmosphere.

With all this in mind, it is felt<sup>42</sup> that if asthmatic children can be helped to bring their resentful feelings out into the open instead of blocking them, many attacks can be eliminated. Even expressing their feelings by crying may help, for it has been shown that if these children can be made to cry, an acute attack may be terminated.

#### SUMMARY

In summary, bronchial asthma probably does have single etiologies, but in most cases there is probably a combination of factors present. The main factors are allergic, infectious, and psychogenic, which theoretically

act in synergism; allergens and infection act directly on the respiratory tree; psychogenic factors act via the hypothalamic-pituitary axis and via the vagus nerve. Concomitant with these, there is postulated a functional suppression of the adrenal cortex, which in times of stress results in a relative deficiency of the glucocorticoid hormones.

The mother is described as narcissistic, dominating, and the strong person in the family. She may overprotect the child, reject him, or both. The father may play a minor role in the family.

The child is sensitive, timid, obsessive, and very dependent, with a tendency to resentment and hostility toward the mother's rejection or to his dependency upon her; he is unable to express his feelings and "bottles them up", setting up emotional tension. He is of average intelligence, but strives for higher goals than he is capable of achieving, and thus adds to his own insecurity. He can be greatly helped if his feelings can be brought into the open.

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## CYSTIC FIBROSIS

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Dr. LoPresti:

Children's Hospital has recently established a clinic‡ for children who have or are suspected of having cystic fibrosis of the pancreas (fibrocystic disease). It is hoped that this clinic will gather together all children with this disease in the Washington metropolitan area and make available to them the necessary laboratory studies and therapeutic agents at a reasonable cost. As the clinic group becomes large enough, certain clinical and basic research will be included. It is to be stressed that the intent of the clinic is not to take over completely the medical supervision of any patient but rather to offer to the referring physician a concentration and quality of facilities and professional advice which the patient could not afford under ordinary circumstances.

Pancreatic Insufficiency	Pulmonary Pathology	Abnormal Sweat	Family History
Steatorrhea	Obstructive emphysema	Salt depletion in hot weather	Siblings with fibrocystic disease
Malnutrition	Chronic bronchopneumonia		
Duodenal assay	Cor pulmonale	Sweat test	
Absent pancreatic enzymes		Increased sweat electrolytes	

FIGURE 1. Diagnosis of fibrocystic disease

Figure 1, which has been adapted from di Sant' Agnese,<sup>1</sup> outlines the diagnostic criteria used in first suspecting and then establishing a diagnosis of fibrocystic disease of the pancreas. The majority of patients with fibrocystic disease will have pancreatic insufficiency and, as a result, will develop steatorrhea with evidence of malnutrition following shortly thereafter. Until the past few years the diagnosis of fibrocystic disease could be established only by performing an analysis of duodenal juice and demonstrating an absent or decreased content of pancreatic enzymes, particularly trypsin.

From discussion at weekly Friday conference.

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At some time during the course of the disease almost all patients have evidence of pulmonary pathology. Such evidence usually takes the form of obstructive emphysema and chronic bronchopneumonia, or repeated bouts of bronchopneumonia. With antibiotic therapy and longer life, some of the patients ultimately die as a result of secondary cardiac involvement, viz., *cor pulmonale*.

It has been shown that patients with fibrocystic disease have an abnormal sweat electrolyte content. Sweat analysis in these patients shows the concentration of sweat sodium and chloride to be three to five times that of the normal individual. As a result, in hot weather affected children may become salt-depleted with accompanying dehydration and heat prostration. Heat prostration may, in fact, be the first sign of the disease.

Finally, a diagnosis of fibrocystic disease of the pancreas is suggested in a child with symptoms in whom there is a family history of the disease. A positive family history, however, is frequently lacking.

Ninety-nine per cent of patients with fibrocystic disease have been shown to have an abnormal sodium and chloride concentration in the sweat. Since the sweat test is such a simple test to perform, it becomes apparent that sweat analysis should be performed in every patient suspected of having the disease. The sweat is analyzed, and if an abnormal electrolyte content is present the diagnosis is almost certain. Rarely, other diseases may give rise to sweat with an abnormal electrolyte content. Such disease entities, however, are always accompanied by an elevated *serum* concentration of electrolyte. If the serum content of sodium and chloride is normal when the concentration of these substances in the sweat is elevated, a diagnosis of fibrocystic disease is virtually certain.

In the majority of children with fibrocystic disease, all the diagnostic criteria previously mentioned will be present. It should be recognized, however, that only one of the criteria may be present in a patient with the disease. There are patients with normal pancreatic function (as evidenced by a normal pancreatic enzyme content in the duodenal juice) who develop only pulmonary manifestations. Such patients will also have an abnormal sweat electrolyte content. Other patients will have signs of pancreatic insufficiency alone, with no evidence of pulmonary pathology. A few cases have had an abnormal duodenal assay for pancreatic enzymes and evidence of pulmonary disease in the presence of a normal concentration of sweat electrolyte.

Recently, di Sant' Agnese<sup>2</sup> has demonstrated that about 5 per cent of patients with fibrocystic disease of the pancreas have clinical evidence of cirrhosis of the liver with or without evidence of portal hypertension. Patients with cirrhosis of the liver and accompanying chronic pulmonary disease in the absence of pancreatic insufficiency have been reported.

Screening tests are sometimes used to suggest a diagnosis of fibrocystic

disease. One widely used test has been the analysis of the stool for trypsin activity. This test is performed by diluting the stool in normal saline and placing single drops of solutions of graduated dilutions on undeveloped x-ray film and noting whether or not the gelatin has been digested. The inference is that trypsin in the stool digests the gelatin. This test has several important drawbacks. First, most patients with fibrocystic disease have been on medication with antibiotics for a prolonged period of time, and, as a result, proteolytic bacteria appear in the stool. Such bacteria will cause gelatin digestion. More important, normal trypsin activity of the duodenal juice averages 250 units whereas as little as one-fifth of a unit of trypsin in the stool will cause gelatin digestion. This test, therefore, will not pick up patients with partial pancreatic insufficiency. For these reasons, analysis of trypsin activity in the stool should be discarded as a screening test for fibrocystic disease of the pancreas.

Microscopic examination of the stool occasionally will provide ancillary information. If the stool of the patient on a normal diet contains an excess of fat droplets, pancreatic insufficiency should be suspected. It should be remembered, however, that a significant number of patients with fibrocystic disease have normal pancreatic activity and, therefore, will have a normal amount of fat in the stool. Other causes of the malabsorption syndrome in the child, e.g., celiac disease, also produce an excess amount of fat in the stool. Normal children on a high fat diet frequently will have apparently abnormal amounts of fat in the stool in the absence of pancreatic insufficiency.

Examination of the viscosity of the duodenal juice is a useful screening test. Even before patients show decreased pancreatic enzyme content of the duodenal juice, the viscosity will increase. This finding is also present in only 70 to 80 per cent of patients with the disease and so, if absent, does not exclude the diagnosis.

Schwachman<sup>3</sup> first suggested the "palm plate" as a screening test for the diagnosis of fibrocystic disease. In our experience in the past year and a half, perhaps for mechanical reasons, the palm plate as a method for determining the amount of sweat chloride has not proved to be a very valuable tool in establishing the diagnosis. In any event, the palm plate is to be considered a screening diagnostic procedure and if the symptoms suggest it, a sweat test should be performed regardless of the result of palm plate testing.

Dr. Parrott:

Cystic fibrosis of the pancreas is a disease in which the clinical manifestations have been well described. Of the etiology, however, little is known. One can go one step back from each of the diagnostic criteria in figure 1 in thinking of the pathogenesis and there he must stop. How may one explain

the disordered physiology leading up to the development of signs of pancreatic and pulmonary insufficiency? A prime factor is that the secretions of both tracheobronchial tree and pancreas, as well as the secretions of exocrine glands throughout the body, tend to be quite viscid. Affected patients also appear to have a peculiar susceptibility to infection with *Staphylococcus aureus*, particularly in the tracheobronchial tree. Thirdly, there is known to be an increased output of sodium and chloride, of potassium to a less constant degree, and even of naturally occurring iodine and thiocyanate in the sweat, tears and saliva. And finally, there is some genetic factor involved.

Proceeding from the above, what are the steps in pathogenesis? The secretions of the tracheobronchial tree are viscid and there is a high susceptibility to infection with Staphylococci. Viscidity plus infection soon cause obstruction, at first minimal but gradually progressing to emphysema and bronchopneumonia. The resultant emphysema and fibrosis may in fact eventually lead to chronic cor pulmonale, some degree of which is present in 20 per cent of cases.

The genetic component is undoubtedly a major factor in the pathogenesis of the disease. Nonetheless it gives no clue to what the underlying biochemical physiological defect is. According to Mendelian laws any child born to a family in which a previous case has occurred has one chance in four of developing the disease. It has been deduced from the reported incidence of the disease that one in twenty persons carries this trait recessively. The incidence has been variously estimated from 1:600 to 1:1000 live births. However, it should be pointed out that it is impossible to predict on the basis of the symptomatology occurring in one child what the symptomatology will be in a subsequently affected sibling.

Over a period of years there have been a number of possible etiologies discussed. Most have been discarded. Viral infection *in utero*, for example, has been dismissed for lack of evidence. Dietary deficiency *in utero* has been suggested. This might bear further investigation since there is some experimental evidence in dogs indicating that on a methionine-free diet, the pregnant dog may produce offspring with pancreatic lesions very closely simulating cystic fibrosis. These animals, however, do not develop clinical disease. Anderson<sup>4</sup> has undertaken a study prescribing a special diet, very high in protein, to mothers who have had one affected child, in an attempt to prevent the development of the disease in subsequent children. In an unofficial review of her first 100 cases she can show no statistical difference in the likelihood of the next child being affected.

What is the defect in the exocrine glands? It is known that there are structural changes, at least at death, in all of the affected glands. There is an eosinophilic staining secretion in the glandular structures. Fibrosis tends

to occur around the glandular ducts. But there is no constant structural defect which in itself explains the physiologic abnormality. In addition the pathology is progressive; it need not be present at birth, for example, in a child dying of meconium ileus. This would seem to lead back to the thought that the pathologic changes result from some other underlying factor.

A disturbance in autonomic function has been postulated, but no histological disturbance in autonomic nervous system fibers can be shown. There is evidence that there is a functional disturbance of those glands which produce the increased amount of sodium. It is not due to increased amount of sodium presented to the gland; these children do not have an increased concentration of serum sodium. A more likely etiologic factor is that the gland is failing to resorb sodium, therefore leading to a greater concentration in the secretion. Another possibility would be increased water resorption in the gland. Whether or not this is under autonomic regulation remains to be determined.

The mucus from the duodenum and from other parts of the body including the saliva has been found by Dische<sup>5</sup> and other workers to contain a material which is an abnormal mucopolysaccharide present in very large amounts. This substance can be found in the secretions of some normal individuals but is not found with the constancy nor in the amount that it is in children with pancreatic fibrosis. This substance precipitates in alcohol and is then insoluble in water. Dische and others have now established to some extent the immunological structure of this substance and have developed a precipitin test to identify it.<sup>6</sup> Whether this will help in the understanding of the disease is still debatable, since it remains to be determined what, if any, abnormality of what enzyme system occurs to explain the presence of this abnormal mucopolysaccharide.

The increased susceptibility to staphylococcal infection in these patients is not the result of chronic lung disease or prolonged antibiotic use. The incidence of recovery of Staphylococci from the lungs of children stricken with cystic fibrosis was, in fact, higher before the era of antibiotics. Since antibiotic therapy for this disease has become a more widespread practice, other organisms are being incriminated in the pathogenesis of the pulmonary infection, and this probably is due to this increased use of antibiotics. It is not known what makes these children peculiarly susceptible to staphylococcal infection. However, it has long been known that the Staphylococcus grows more readily in media with a high chloride content. And at least in a few tested individuals, an increased sodium and chloride content of the bronchial secretions (as well as the sweat, saliva and tears) has been found.

There is little doubt that intensive research is needed before we can better answer some of these questions. In the meanwhile it is vital that physicians recognize the symptoms and secure the diagnosis of cystic fibrosis in affected

children. Detailed and careful medical attention can prolong their lives and save the lives of some.

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#### GANGRENOUS PURPURA ASSOCIATED WITH MENINGOCOCCEMIA

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Several different types of skin lesions are found in patients with septice-mia due to the meningococcus organism. Costello<sup>1</sup> emphasizes the following five types: (1) erythema nodosum-like lesions such as those seen in patients with rheumatic fever and in eruptions due to drugs, (2) punctate petechiae which are interspersed with large hemorrhagic blotches, occasionally associated with subconjunctival and mucosal hemorrhages, (3) lesions which resemble "fleabites," containing a central hemorrhagic area surrounded by a faint erythematous zone, produced by septic vascular thrombi, and resembling those seen in patients with Rocky Mountain spotted fever, (4) irregular round hemorrhages with gun-metal colored centers composed of pus cells, and (5) necrotic lesions which are depressed beneath the surface of the skin.

The so-called "fulminant" forms of meningococcal septicemia often present with massive purpuric hemorrhages, and the regions so involved may become gangrenous. The case presented here is that of a patient in whom the clinical features were those commonly seen in meningococcal septicemia which could not be proved bacteriologically, but in whom gangrenous purpura developed.

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## CASE REPORT

This was the first hospital admission for V. M. D., a 14 year old Negro girl who had been well until one week prior to her admission, at which time she had the onset of a cold and "sore throat" for which she was treated symptomatically. No fever had been present, but she did complain of a diffuse headache and some pain "in her eyes" at various times. On the day prior to her admission, she began to have chills, fever and vomiting. She was seen by a private physician who administered two injections of 600,000 units of penicillin, and prescribed oral tetracycline which she received twice that day. The patient did not improve. Three episodes were described in which she was delirious, following which she became completely flaccid. This was accompanied by involuntary urination, defecation and frothing at the mouth. Just prior to admission, the patient had a convulsive seizure.

The past history, system review, and family history were noncontributory.

On examination, the patient was a well-developed, somewhat obese Negro adolescent girl who was disoriented and hallucinating actively. The temperature was 103° F. by rectum, pulse rate 160 per minute, and respirations 40 per minute; the blood pressure was 110/70. Pertinent findings were as follows: palpable posterior cervical nodes, moderate nuchal rigidity, and positive Brudzinski's and Kernig's signs.

Initial laboratory determinations showed a white blood cell count of 17,500 cells per cu. mm., with 88 per cent neutrophils, 7 per cent band forms, 1 per cent young forms and 4 per cent mature lymphocytes. The hemoglobin was 9.1 Gm. per 100 ml. and the hematocrit 36 per cent. The urinalysis was normal. A lumbar puncture was done shortly after admission. The spinal fluid was slightly cloudy and there were 150 cells present; 90 per cent were neutrophils and 10 per cent lymphocytes. The protein content was 54 mg. per 100 ml. and the sugar was 98 mg. per 100 ml.

Approximately eight hours after her admission the patient became critically ill. Her blood pressure dropped to 86/40, and her pulse rate was 130 per minute. Rapidly developing skin manifestations, which consisted of multiform purpuric lesions, first appeared on her lower extremities and then progressed to her upper extremities with only rare lesions on the trunk. Two subconjunctival hemorrhages appeared. Some of the purpuric lesions rapidly became confluent, especially one such lesion on her right great toe. The Rumpel-Leede test was negative. The prothrombin time was normal. The bleeding time was normal. The circulating eosinophil count was zero. The Lee-White clotting time was five minutes. The clot retraction was adequate. A smear of one of the petechial lesions failed to reveal the presence of any organisms.

Because of the findings of pleocytosis in the spinal fluid, the occurrence of embolic phenomena (purpura), a lowered blood pressure and a critically ill patient who was semicomatose, it was felt that the patient had a septicemia, probably due to the meningococcus organism, with an accompanying early Waterhouse-Friderichsen syndrome, and she was treated as such. Intravenous antibiotics were immediately begun, and included chloramphenicol monosuccinate, sulfadiazine and aqueous penicillin. One dose of an intravenous adrenal cortical steroid preparation was also given immediately.

The patient remained in this critical condition for approximately 20 hours after which she started to become rational. Since the circulating eosinophile count, which was done every six hours, was always zero, no further steroids were given. Seventy-two hours after the appearance of the purpura, the patient began taking fluids orally. The intravenous medications and maintenance electrolyte fluids were discontinued and she was then given regular oral feedings and intramuscular antibiotics. She was

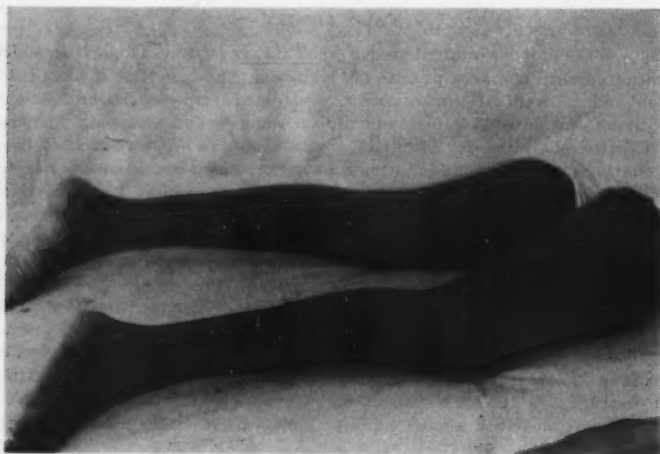


FIG. 1. Healing gangrenous lesions on lower extremities

no longer disoriented. During these first 72 hours of hospitalization, both the upper and lower extremities were noted to become gradually edematous. The purpuric lesions themselves were also noted to become edematous, slowly changing in color to purple and eventually to black. The patient complained of pain in all extremities.

Cultures of blood and spinal fluid obtained on admission were sterile; throat culture did not demonstrate any abnormal organisms.

The black skin lesions gradually became gangrenous and began to demarcate very slowly during the following two weeks. The edema of the extremities and the concomitant pain also gradually subsided. Surgical excision of one of the skin lesions was done. This was examined microscopically and was found to show an acute inflammatory reaction only.

Fifteen days after the appearance of the purpuric lesions, the systemic antibiotics were discontinued. Local treatment of the gangrenous lesions was then carried out. This included repeated washing with a weakly antiseptic solution followed by the application of bacitracin ointment. The lesions slowly began to slough and new granulation tissue was apparent beneath the sloughs (see figure 1). Healing occurred gradually and required about seven or eight weeks for the entire process. Only one gangrenous lesion failed to heal; part of the distal phalanx of the large toe of the right foot became entirely gangrenous, necessitating amputation after adequate demarcation had occurred. The patient was discharged, fully recovered, 10 weeks after admission. She was seen subsequently in the surgical clinic until the area of amputation was completely healed.

#### DISCUSSION

Gangrenous purpura is decidedly a rare occurrence, as was shown by Dunn<sup>2</sup> in his rather extensive study several years ago. He was unable to find more than 10 documented and proven cases of gangrenous purpura

occurring in meningococcal septicemia from 1915 to 1950. Weiner,<sup>2</sup> in an independent study, reported a case of gangrene of the extremities in a patient with meningococcal septicemia. His review of the literature revealed 9 other such cases, 4 of which had appeared in the review of Dunn. Interestingly enough, in *all* the cases which Weiner reviewed, gangrene of the skin was present as well as gangrene of the digits and the extremities. It is felt that gangrene of the digits and the extremities represents a special instance of cutaneous gangrene.

Both sexes were equally affected. Age distribution ranged from 4½ months to 34 years, with 70 per cent of the cases occurring in patients under the age of 7 years.

#### *Etiology*

Gangrenous purpura, *per se*, is now thought in most cases to result from a septicemic process in which any one of a number of organisms may be responsible. The two most important of these organisms are the meningococcus and the Streptococcus. Idiopathic cases are also encountered in which no evidence of a systemic process can be found and in which no underlying primary disease can be demonstrated. In a few cases, manifestations of anaphylaxis such as joint swellings, and leukocytosis in the absence of fever, have been found. Finally, some cases have been described in patients recovering from measles and scarlet fever.<sup>1</sup>

#### *Pathology*

The skin lesions of gangrenous purpura can be explained on the basis of damage to the endothelial lining of the arterioles by the meningococci, causing an inflammatory reaction in the vessel wall with ensuing necrosis, thrombosis and extravasation of blood and fluid. Hill and Kinney<sup>4</sup> have examined carefully and described in detail sections of these gangrenous lesions in patients with meningococcal septicemia who died and on whom postmortem examinations were carried out. Specifically, there is diffuse dilatation and engorgement of the blood vessels throughout the depth of the cutaneous lesions. This vascular damage is not restricted to the skin, inasmuch as autopsy findings have shown the same changes throughout the serous surfaces and other organs of the body. As far as the smaller blood vessels and the capillaries are concerned, there is swelling of the endothelial cells, often to such a degree that the continuity of the lining endothelium is broken. Subsequently necrosis of these cells occurs. Red blood cell diapedesis then follows, causing small perivascular hemorrhages and larger lakes of red cells. Rapidly following this process, polymorphonuclear leukocytes are found lying free in the lumen and infiltrating the area of vascular damage. Many platelet thrombi are seen in the smaller vessels.

Several rather basic factors are postulated in an attempt to account for the pathologic findings, none of which individually could be accepted as the only cause. First, any factors which tend to increase the agglutinability of the blood may precipitate or predispose to the formation of intravascular thrombi. Second, any factors which tend to cause sludging of the blood may account for the slowdown of blood flow and the eventual blockage to the circulation of the blood in the smaller vessels. This process causes much damage to the tissues. Third, arterial and arteriolar spasm accounts for temporary diminution or depletion of the blood supply to the tissue involved. If this spasm is unduly prolonged, anoxemia and death of tissue shortly ensue. It is thought that the factors of sludging and spasm play a major role in the production of gangrenous purpura when shock is present; they are also thought to be prominent in the production of gangrene of the digits and the extremities. Finally, the meningococcus is known to produce both an endotoxin and an exotoxin. It has been shown that there is direct localization of these toxins in the endothelial cells, causing inflammation, thrombosis and necrosis. It is because of this latter finding that many observers feel the Schwartzman phenomenon plays a large part in the process of damage to the tissues. In his experiment, Schwartzman inoculated rabbits intradermally with the filtrate of a meningococcal culture and followed this with an intravenous injection of the same filtrate 24 hours later; this produced a hemorrhagic and subsequent necrotic skin lesion at the site of the original intradermal injection. Black-Shaffer, Hiebert and Kerby<sup>5</sup> proposed the Schwartzman phenomenon as the underlying process in patients with gangrenous purpura of idiopathic etiology.

#### *Clinical Course*

Four clinical phases are described in the production of gangrenous purpura:<sup>3</sup>

1. *The phase of appearance and generalization.* The majority of the lesions of gangrenous purpura are initially port wine in color, and subsequently become purple or violet. This phase occurs within the first 48 hours.

2. *The phase of necrosis.* Blisters form on the surface of the initial purpuric lesions. These discharge serous or sanguinous fluid and eventually form a plaque of necrotic tissue. This phase occurs within four or five days after the initial lesions appear.

3. *The phase of separation of sloughs.* The plaque of necrotic tissue soon becomes black and slowly demarcates sharply from the surrounding healthy skin, forming the eschar. The eschar usually involves skin and subcutaneous tissue. This phase occurs during the second to fourth week of illness.

4. *The phase of repair.* The eschar falls off, leaving a raw granulating

surface which heals slowly during the fifth to eighth week, with the formation of considerable scar tissue.

An analysis of all the cases of gangrenous purpura thus far reviewed in the literature reveals that *severe* meningococcemia has been present each time. The progression of the gangrene has not been stopped by the antibiotic agents used systemically to treat the septicemia, despite the fact that there has been general clinical improvement on the part of the patient. It is also interesting to note that approximately 70 per cent of the cases have occurred since 1940. This might be explained on the basis of the advent of the antibiotic agents, since, prior to the antibiotic era, fulminant meningococcemia resulted most often in death *before* the gangrenous lesions could become manifest.

#### *Treatment*

Appropriate therapy of the underlying causative condition must be carried out first. This involves vigorous systemic antibiotic therapy in meningococcal septicemia and the addition of adrenal cortical steroids should the signs of Waterhouse-Friderichsen syndrome appear.

As far as the gangrenous skin lesions themselves are concerned, it is essential to prevent the propagation of these gangrenous areas; this occurs rather easily when these areas are exposed to pressure for prolonged periods of time. Thus, the position of the patient in bed must be changed as frequently as possible. All means should also be utilized toward prevention of secondary infection. This may be accomplished by adequate debridement of all the necrotic areas, frequent washings with saline or mildly antiseptic agents, and the *local* application of an antibiotic, inasmuch as the bacteria present in the sloughs may be insensitive to the systemic antibiotics being used. Georgiade, et al.,<sup>6</sup> feel that the necrosis of scattered cutaneous areas is best handled by excision and early skin grafting which shortens considerably the period of convalescence. Of course, amputation must be done in those cases in which the gangrene involves the digits or greater portions of an extremity.

#### SUMMARY

Gangrenous purpura developed in a 14 year old Negro girl with presumed meningococcemia.

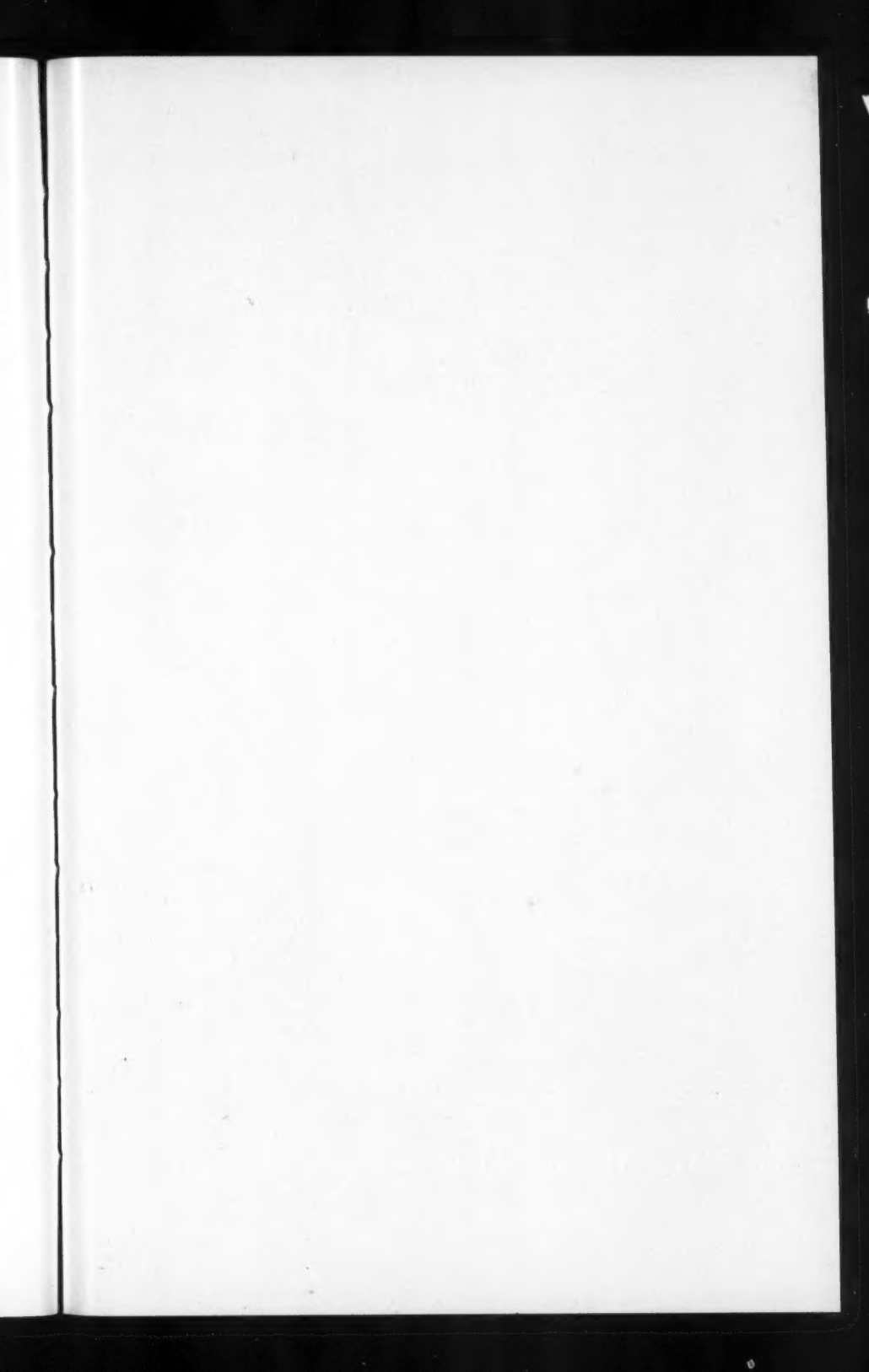
Such a complication is a rare occurrence.

Pathologically, gangrenous purpura is explained on the basis of damage to the endothelial lining of the arterioles, with resultant inflammation, thrombosis and necrosis of living tissue. It is also felt that the Shwartzman phenomenon plays a large part in damaging tissues.

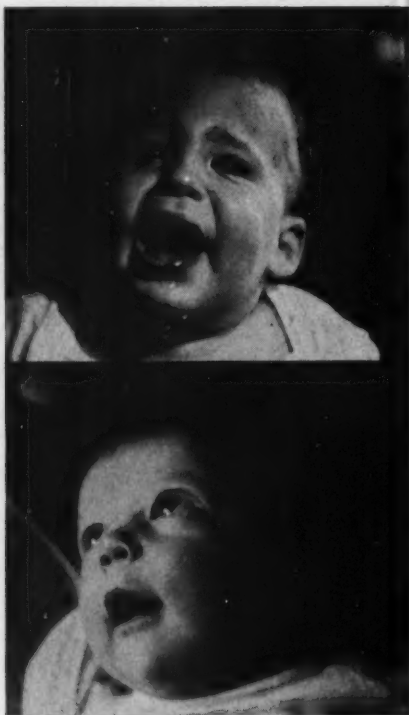
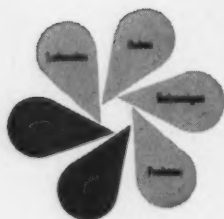
The treatment of gangrenous purpura is first, to attack the underlying cause, and second, to prevent secondary infection of the gangrenous skin by adequate debridement and local antibiotic application. Amputation may be necessary in cases of gangrene of the digits or the extremities.

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